EXHIBIT 4

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-723/S-017

RECEIVED
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D-491, RTC

JUN 16 1995

Abbott Laboratories
Pharmaceutical Product Division
Attention: Mr. James D. Steck
One Abbott Park Road
Abbott Park, Illinois 60064-3500

Dear Mr. Steck:

Please refer to your supplemental new drug application dated June 30, 1994, submitted under Section 505(b) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.70(b)(3) for Depakote® (divalproex sodium) Tablets for prophylaxis of migraine headache.

We also acknowledge receipt of your additional amendments and communications dated:

August 4, 1994	September 2, 1994	September 7, 1994
September 15, 1994	September 16, 1994	September 28, 1994
October 7, 1994	October 11, 1994	October 28, 1994
October 31, 1994	February 9, 1995	

We have completed our review of this application and find that it is approvable for the indication, prophylaxis of migraine headache, provided:

1. That you satisfy a number of ordinary regulatory requirements enumerated elsewhere in this letter,

2. That Depakote® Tablets are marketed under the labeling text attached to this letter, and

3. That there is in place, prior to the initial distribution of Depakote® Tablets as a treatment for migraine, a mechanism/system to ensure that migraineurs receiving prescriptions for Depakote® Tablets for migraine prophylaxis will be provided with an information sheet that provides, in language readily understandable to a lay person, i) a clear and unambiguous warning that valproate is a known human teratogen and, ii) an explication of the potential risks this property of the drug imposes upon women who elect to use the product during their childbearing years.

An explication of the basis for our decision.

We are mindful that valproate containing products have long been marketed for use in the management of epilepsy, and more recently for the management of acute mania, without a requirement for a patient information sheet that calls attention to the drug's teratogenic potential. Drug product labeling, however, must provide information critical to the prudent use of a product for each of the indications for which it is recommended. What constitutes critical information is not an isolated function of the properties of the drug product, but the characteristics of the illness the product is intended to treat, and the nature of the population who suffer from that illness.

Epilepsy and acute mania are potentially life-endangering illnesses; immediate control of their manifestations is vital to the well being of the patient. In contrast, migraine, albeit a chronic, painful, life-disrupting illness, is neither life-threatening nor life-endangering. Moreover, several marketed drug products are available that can effectively and safely abort acute migrainous attacks.

In short, the risk benefit considerations impinging upon the use of Depakote® Tablets in migraine prophylaxis differ substantively from those affecting its use in epilepsy and mania.

Beyond the nature of the illness being treated, the characteristics of the patient population who will be exposed to Depakote® Tablets once it is marketed for use in the prophylaxis of migraine has also influenced our decision.

Migraine is predominantly an illness of women in their childbearing years. Accordingly, the widespread use of Depakote® Tablets by migraineurs will be likely to lead to an increased use of the product in women and this, given valproate's teratogenic potential, may have untoward consequences for some of them, unborn children they may carry, and for the public health.

In light of these considerations, a case could be made that it is not in the overall interest of the public health to approve Depakote® Tablets for use in migraine prophylaxis. We have considered this argument and rejected it. We not only find it needlessly paternalistic, but unlikely to reduce the very risk it would be intended to affect: elimination of valproate's use by women of childbearing potential. Depakote® Tablets and other valproate containing marketed products are currently, and are likely to continue to be, used widely for the prophylaxis of migraine.

On the other hand, we are obliged to ensure that all reasonable steps are taken to reduce the likelihood of avoidable injury that arises from the use of a marketed drug product. Specifically, if Depakote® Tablets are to be marketed and promoted for use in the management of migraine, we are obliged to ensure that those who undertake to use the product are as fully informed about the risks of that treatment as possible. The critical issue, of course, is in how best to accomplish that goal.

Typically, where prescription drug products are concerned, the agency relies on the prescriber to inform the patient about the risks that may be associated with the use of a product. In some cases, professional product labeling includes specific suggestions about information that it is deemed useful to provide to the patient. There are occasions, however, when, by nature of the risk or the population involved, these ordinary mechanisms are deemed inadequate (e.g., with Accutane®, with Imitrex® Injection, etc) and information sheets advising of serious risks or special precautions needed to ensure the safe use of a drug product are provided directly to the patient.

It is our judgment that, for Depakote® Tablets to be used safely in the prophylaxis of migraine, there must be a reliable means to inform patients directly, before they begin a course of treatment, about its teratogenic potential. Accordingly, we are requiring that a patient information sheet and a system to deliver it to women contemplating the chronic use of Depakote® Tablets in migraine prophylaxis be in place before distribution of the product for this use commences.

Toward this same goal, we are requesting that you make additional changes to the text of Depakote® Tablet labeling.

We have, among other modifications, added a second box warning advising that valproate is a known teratogen in humans and is capable of causing neural tube defects such as spina bifida. Again, the aim of this box warning is to enhance the likelihood that prescribers and patients will be fully informed of valproate's teratogenic potential and will weigh that potential risk against the expected benefit of Depakote® Tablets as a prophylactic treatment for migraine.

Regarding the draft labeling attached to this letter, when specific wording is employed, please use the text verbatim, save for minor matters of grammar or style. Additional requests for proposed wording are embedded within the text of the proposed labeling. Also, please revise the draft labeling to include those important adverse events not currently in labeling but reported since your last safety update.

As to the patient information sheet, we are prepared to work with you to develop an appropriate text for, and system for its delivery.

FOREIGN REGULATORY UPDATE/LABELING

We require a review of the status of all actions taken or pending before foreign regulatory authorities on all dosage forms of Depakote®. Approval actions can be noted, but we ask that you describe in detail any and all actions taken that have been negative, supplying a full explanation of the views of all parties and the resolution of the matter. In addition, we ask that you provide us current foreign labeling for divalproex sodium, along with the English translations when needed. If divalproex sodium labeling is uniform worldwide, it would, of course, be sufficient to provide only the English translation of that standard labeling.

UPDATE OF LITERATURE

Please review and provide a summary of all published reports bearing on the safety and effectiveness of divalproex sodium that have appeared since your last comprehensive review. Please alert us to any reports of adverse events or reactions that have not previously been reported in association with its use.

SAFETY UPDATE

Please submit a safety update. In the update, please include only a cumulative report of serious adverse events and deaths, as well as any other adverse events, serious or not, that have not been previously reported.

MANUFACTURING AND CONTROLS

The review of the Environmental Assessment has not been completed at this time. We expect your cooperation in resolving any problems.

MISCELLANEOUS

Please submit fifteen copies of the printed labels and other labeling, ten of which are individually mounted on heavy weight paper or similar material.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Neuropharmacological Drug Products and two copies of both the promotional material and package insert to, directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications
HFD-240, Room 17B-17
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, or notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of such action, the FDA may take action to withdraw the application.

Under section 736(a)(1)(B)(ii) of the Prescription Drug User Fee Act of 1992, this letter triggers the remaining 50% of the fee assessed for this application. You will receive an invoice for the amount due within the next month. Payment will be due within 30 days of the date of this invoice.

In accordance with the policy described in 21 CFR 314.102(d) and in the Center for Drug Evaluation and Research Staff Manual Guide CDB 4820.6, you may request an informal conference with the Division to discuss what further steps you need to secure approval. The meeting is to be requested at least 15 days in advance. Alternatively, you may choose to receive such a report via a telephone call. Should you wish this conference or a telephone report, or should any questions arise concerning this NDA, please contact Mr. Donald Grilley, Regulatory Management Officer, at (301) 594-2777.

The drug may not be legally marketed for the indication provided by this application until you have been notified in writing that the application is approved.

Sincerely yours,

Paul Leber, M.D.
Director
Division of Neuropharmacological
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ATTACHMENT